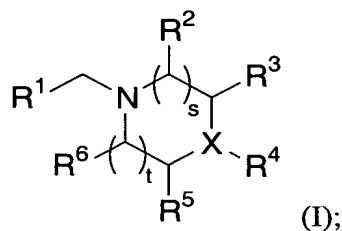


WHAT IS CLAIMED IS:

1. A process for preparing a compound of Formula (I):



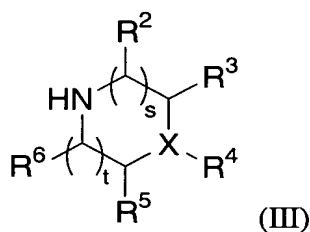
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which comprises:

- (A) reacting an aldehyde of Formula (II):

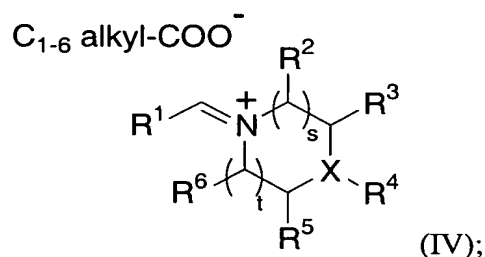


with a cyclic amine compound of Formula (III):



10

in an organic solvent and in the presence of a C<sub>1-6</sub> alkylcarboxylic acid and with removal of by-product water, to form a reaction mixture comprising an iminium salt of Formula (IV):



15

- (B) adding a tetrahydroborate salt to the reaction mixture of Step A to obtain a product comprising a compound of Formula (I) and one or more borane complexes thereof; and

(C) treating the product of Step B with a catalyst selected from the group consisting of Pt oxide, Pt halide, Pd oxide and Pd halide in the presence of an alcohol to cleave the one or more borane complexes and thereby obtain the compound of Formula (I) substantially free of any borane complex thereof;

5

wherein:

X is CH or N;

10 R<sup>1</sup> is a heteroaryl which is (i) a 5- or 6-membered heteroaromatic ring or (ii) a 9- or 10-membered fused, bicyclic ring system in which both rings are aromatic rings and at least one of the rings is a heteroaromatic ring; wherein the heteroaryl contains at least one carbon atom, one or more nitrogen atoms, optionally one or more O atoms, and optionally one or more S atoms; wherein at least one ring nitrogen in the heteroaryl has an unbonded electron pair that is not  
15 utilized in the aromatic  $\pi$  system of the heteroaryl; and wherein the heteroaryl is optionally substituted with from 1 to 5 substituents each of which is independently:

- (1) halo,
- (2) -C<sub>1-6</sub> alkyl,
- (3) -C<sub>1-6</sub> alkyl mono-substituted with -OH, -O-C<sub>1-6</sub> alkyl, -CO<sub>2</sub>R<sup>a</sup>,  
20 -S(=O)R<sup>c</sup>, or -SO<sub>2</sub>R<sup>c</sup>,
- (4) -O-C<sub>1-6</sub> alkyl,
- (5) -O-C<sub>1-6</sub> alkyl mono-substituted with -OH, -O-C<sub>1-6</sub> alkyl, -CO<sub>2</sub>R<sup>a</sup>,  
-S(=O)R<sup>c</sup>, or -SO<sub>2</sub>R<sup>c</sup>,
- (6) -OH,
- (7) -CO<sub>2</sub>R<sup>a</sup>,
- (8) -C(=O)N(R<sup>a</sup>R<sup>b</sup>),
- (9) -S(=O)R<sup>c</sup>,
- (10) -SO<sub>2</sub>R<sup>c</sup>,
- (11) aryl, optionally substituted with from 1 to 5 substituents each of which is  
25 independently halo, -OH, -C<sub>1-6</sub> alkyl, -O-C<sub>1-6</sub> alkyl, -CO<sub>2</sub>R<sup>a</sup>, -S(=O)R<sup>c</sup>,  
or -SO<sub>2</sub>R<sup>c</sup>,
- (12) -C<sub>1-6</sub> alkyl-aryl, wherein the aryl is optionally substituted with from 1 to 5  
30 substituents each of which is independently halo, -OH, -C<sub>1-6</sub> alkyl,  
-O-C<sub>1-6</sub> alkyl, -CO<sub>2</sub>R<sup>a</sup>, -S(=O)R<sup>c</sup>, or -SO<sub>2</sub>R<sup>c</sup>,

- (13) HetA, or
- (14) -C<sub>1-6</sub> alkyl-HetA;

each of R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup> and R<sup>6</sup> is independently:

- 5 (1) -H,
- (2) -C<sub>1-6</sub> alkyl,
- (3) -C<sub>1-6</sub> alkyl mono-substituted with -OH, -O-C<sub>1-6</sub> alkyl, -CO<sub>2</sub>R<sup>a</sup>,  
-S(=O)R<sup>c</sup>, or -SO<sub>2</sub>R<sup>c</sup>,
- (4) -O-C<sub>1-6</sub> alkyl,
- 10 (5) -O-C<sub>1-6</sub> alkyl mono-substituted with -OH, -O-C<sub>1-6</sub> alkyl, -CO<sub>2</sub>R<sup>a</sup>,  
-S(=O)R<sup>c</sup>, or -SO<sub>2</sub>R<sup>c</sup>,
- (6) -OH,
- (7) -CO<sub>2</sub>R<sup>a</sup>,
- (8) -C(=O)N(R<sup>a</sup>R<sup>d</sup>),
- 15 (9) -S(=O)R<sup>c</sup>,
- (10) -SO<sub>2</sub>R<sup>c</sup>,
- (11) aryl, optionally substituted with from 1 to 5 substituents each of which is  
independently halo, -OH, -C<sub>1-6</sub> alkyl, -O-C<sub>1-6</sub> alkyl, -CO<sub>2</sub>R<sup>a</sup>, -S(=O)R<sup>c</sup>,  
or -SO<sub>2</sub>R<sup>c</sup>,
- 20 (12) -C<sub>1-6</sub> alkyl-aryl, wherein the aryl is optionally substituted with from 1 to 5  
substituents each of which is independently halo, -OH, -C<sub>1-6</sub> alkyl,  
-O-C<sub>1-6</sub> alkyl, -CO<sub>2</sub>R<sup>a</sup>, -S(=O)R<sup>c</sup>, or -SO<sub>2</sub>R<sup>c</sup>,
- (13) HetA, or
- (14) -C<sub>1-6</sub> alkyl-HetA;

R<sup>4</sup> is:

- (1) -H,
- (2) -C<sub>1-20</sub> alkyl, which is:
  - 30 (a) optionally substituted with from 1 to 7 substituents each of which  
is independently:
    - (i) -OH,
    - (ii) -C<sub>1-6</sub> alkyl,
    - (iii) -O-C<sub>1-6</sub> alkyl,
    - (iv) -CO<sub>2</sub>R<sup>a</sup>,

(v)  $-C(=O)N(R^aR^b)$ ,

(vi)  $-S(=O)R^c$ , or

(vii)  $-SO_2R^c$ , and

(b) optionally substituted with from 1 to 3 substituents each of which is independently:

(i)  $-R^k$ ,

(ii)  $-C_{1-6}$  alkyl- $R^k$ ,

(iii)  $-C(=O)-R^k$ , or

(iv)  $-C(=O)N(R^a)R^k$ , or

(3)  $-R^k$ ;

each  $R^a$  and  $R^b$  is independently  $-H$  or  $-C_{1-6}$  alkyl;

each  $R^c$  is independently  $-C_{1-6}$  alkyl;

each  $R^d$  is independently  $-H$ ,  $-C_{1-6}$  alkyl or  $-C_{1-6}$  haloalkyl;

each  $R^k$  is independently an optionally substituted carbocycle or an optionally substituted heterocycle;

carbocycle in  $R^k$  is independently (i) a  $C_3$  to  $C_8$  monocyclic, saturated or unsaturated ring, (ii) a  $C_7$  to  $C_{12}$  bicyclic ring system, or (iii) a  $C_{11}$  to  $C_{16}$  tricyclic ring system, wherein each ring in (ii) or (iii) is independent of, fused to, or bridged with the other ring or rings and each ring is saturated or unsaturated; wherein the carbocycle is optionally substituted with from 1 to 7 substituents each of which is independently

(1) halogen, provided that the ring of the carbocycle substituted with the halogen is aromatic,

(2)  $-OH$ ,

(3)  $-C_{1-6}$  alkyl, optionally mono-substituted with  $-OH$ ,  $-O-C_{1-6}$  alkyl,  $-CN$ ,  $-NO_2$ ,  $-C(=O)N(R^aR^b)$ ,  $-CO_2R^a$ ,  $-S(=O)R^c$ ,  $-SO_2R^c$ ,  $-SO_2N(R^aR^b)$ ,  $-N(R^a)SO_2R^c$ ,  $-C_{3-8}$  cycloalkyl, phenyl,  $-O$ -phenyl, or HetB,

(4)  $-C_{2-6}$  alkenyl,

(5)  $-C_{2-6}$  alkynyl,

(6)  $-O-C_{1-6}$  alkyl,

- (7) -CN,  
 (8) -NO<sub>2</sub>,  
 (9) -C(=O)N(R<sup>a</sup>R<sup>b</sup>),  
 (10) -CO<sub>2</sub>R<sup>a</sup>,  
 5 (11) -S(=O)R<sup>c</sup>,  
 (12) -SO<sub>2</sub>R<sup>c</sup>,  
 (13) -N(R<sup>a</sup>)SO<sub>2</sub>R<sup>c</sup>,  
 (14) -SO<sub>2</sub>N(R<sup>a</sup>R<sup>b</sup>),  
 (15) -C<sub>3-8</sub> cycloalkyl,  
 10 (16) phenyl,  
 (17) -O-phenyl, or  
 (18) HetB;

heterocycle in R<sup>k</sup> is independently (i) a 4- to 8-membered, saturated or unsaturated monocyclic  
 15 ring, (ii) a 7- to 12-membered bicyclic ring system, or (iii) an 11 to 16-membered tricyclic ring  
 system; wherein each ring in (ii) or (iii) is independent of or fused to the other ring or rings and  
 each ring is saturated or unsaturated; wherein the monocyclic ring, bicyclic ring system, or  
 tricyclic ring system contains from 1 to 6 heteroatoms independently selected from N, O and S;  
 wherein any one or more of the nitrogen and sulfur heteroatoms is optionally oxidized, and any  
 20 one or more of the nitrogen heteroatoms is optionally quaternized; and wherein the heterocycle is  
 optionally substituted with from 1 to 7 substituents each of which is independently

- (1) halogen, provided that the ring of the heterocycle substituted with the halogen is  
 aromatic,  
 (2) -OH,  
 25 (3) -C<sub>1-6</sub> alkyl, optionally mono-substituted with -OH, -O-C<sub>1-6</sub> alkyl, -CN, -NO<sub>2</sub>,  
 -C(=O)N(R<sup>a</sup>R<sup>b</sup>), -CO<sub>2</sub>R<sup>a</sup>, -S(=O)R<sup>c</sup>, -SO<sub>2</sub>R<sup>c</sup>, -SO<sub>2</sub>N(R<sup>a</sup>R<sup>b</sup>), -N(R<sup>a</sup>)SO<sub>2</sub>R<sup>c</sup>,  
 -C<sub>3-8</sub> cycloalkyl, phenyl, -O-phenyl, or HetB,  
 (4) -C<sub>2-6</sub> alkenyl,  
 (5) -C<sub>2-6</sub> alkynyl,  
 30 (6) -O-C<sub>1-6</sub> alkyl,  
 (7) -CN,  
 (8) -NO<sub>2</sub>,  
 (9) -C(=O)N(R<sup>a</sup>R<sup>b</sup>),  
 (10) -CO<sub>2</sub>R<sup>a</sup>,

- (11)  $-S(=O)R^c$ ,
- (12)  $-SO_2R^c$ ,
- (13)  $-N(R^a)SO_2R^c$ ,
- (14)  $-SO_2N(R^aR^b)$ ,
- 5 (15)  $-C_{3-8}$  cycloalkyl,
- (16) phenyl,
- (17)  $-O$ -phenyl, or
- (18) HetB;

10 and with the proviso that (a) when a ring nitrogen is part of a non-aromatic ring in  $R^k$ , the nitrogen is a tertiary amine or is quaternized and (b) when a ring sulfur is part of a non-aromatic ring and is attached to ring carbons in  $R^k$ , the sulfur is a sulfoxide ( $-S(=O)-$ ) or a sulfone ( $-S(O_2)-$ );

15 each HetA is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 3 heteroatoms independently selected from O and S, wherein the heteroaromatic ring is optionally fused with a benzene ring; wherein the optionally fused heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently halo,  $-C_{1-6}$  alkyl, or  $-O-C_{1-6}$  alkyl;

20 each HetB is independently a 5- or 6-membered saturated or unsaturated heterocyclic ring containing from 1 to 4 heteroatoms independently selected from N, O and optionally oxidized S, wherein the heterocyclic ring is optionally fused with a benzene ring; and wherein the optionally fused heterocyclic ring is optionally substituted with from 1 to 7 substituents each of which is independently halogen, provided that the ring to which the halogen is attached is aromatic,  $-C_{1-6}$  alkyl,  $-O-C_{1-6}$  alkyl, or  $-CO_2R^a$ ; and with the proviso that when HetB is not aromatic, then any  
25 ring nitrogen is a tertiary amino nitrogen and any ring sulfur that is attached to ring carbons is a sulfoxide or a sulfone; and

s and t are each an integer equal to zero or 1, with the proviso that  $s + t = 1$  or 2.

30 2. The process according to claim 1, wherein by-product water is removed from the reaction mixture of Step A by conducting Step A in the presence of a dehydrating agent.

3. The process according to claim 1, wherein the solvent employed in Step A is an aprotic solvent.

4. The process according to claim 1, wherein Step A is conducted at a temperature in the range of from about 0 to about 30°C.

5. The process according to claim 1, wherein aldehyde II is employed in Step A in an amount in the range of from about 1 to about 5 moles per mole of cyclic amine III.

6. The process according to claim 1, wherein the C<sub>1-6</sub> alkylcarboxylic acid is employed in Step A in an amount in the range of from about 1 to about 3 equivalents per equivalent of amino groups present in cyclic amine III.

7. The process according to claim 1, wherein the tetrahydroborate salt added in Step B is an alkali metal salt or a quaternary ammonium salt of tetrahydroborate.

8. The process according to claim 1, wherein the tetrahydroborate salt is added in Step B in an amount in the range of from about 0.8 to about 5 moles per mole of cyclic amine III.

9. The process according to claim 1, wherein Step B is conducted at a temperature in the range of from about 0 to about 30 °C

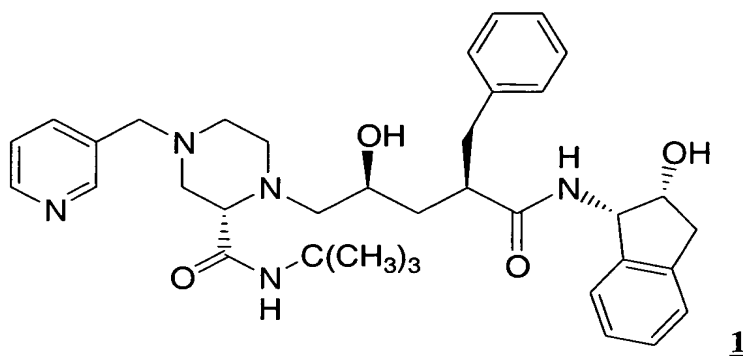
10. The process according to claim 1, wherein the catalyst in Step C is employed in an amount in the range of from about 0.01 to about 0.2 moles per mole of cyclic amine III.

11. The process according to claim 1, wherein the alcohol employed in Step C is a C<sub>1-6</sub> alkyl alcohol.

12. The process according to claim 1, wherein the alcohol employed in Step C is employed in an amount of at least about 3 moles per mole of borane complex in the Step B product.

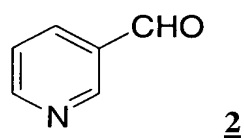
13. The process according to claim 1, wherein Step C is conducted at a temperature in the range of from about 0 to about 50°C.

14. A process for preparing Compound 1:

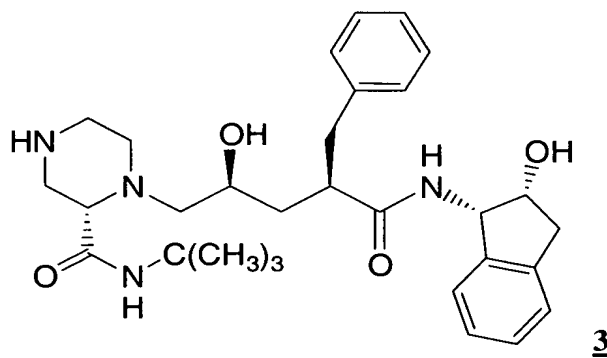


which comprises:

(A) reacting aldehyde 2:

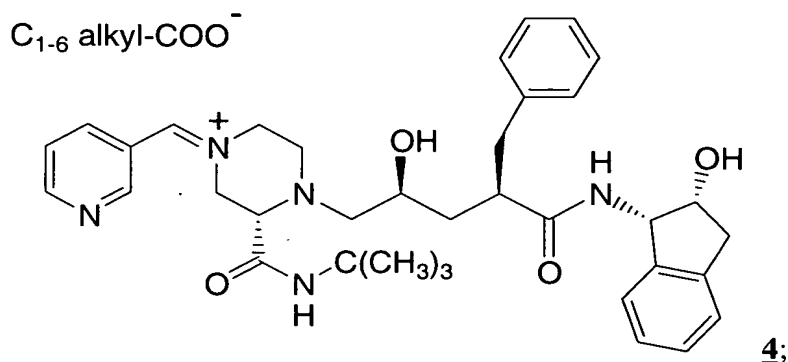


10 with piperazine 3:



in an organic solvent and in the presence of a C<sub>1-6</sub> alkylcarboxylic acid and with removal of by-product water, to form a reaction mixture comprising an iminium salt 4:





(B) adding a tetrahydroborate salt to the reaction mixture of Step A to obtain a product comprising Compound 1 and one or more borane complexes thereof; and

5 (C) treating the product of Step B with a catalyst selected from the group consisting of Pt oxide, Pt halide, Pd oxide and Pd halide in the presence of a  $C_{1-6}$  alkyl alcohol to cleave the one or more borane complexes and thereby obtain Compound 1 substantially free of any borane complex thereof.

10 15. The process according to claim 14, wherein:  
 by-product water is removed from the reaction mixture of Step A by conducting Step A in the presence of a dehydrating agent;  
 the solvent employed in Step A is an aprotic solvent;  
 Step A is conducted at a temperature in the range of from about 0 to about 30 °C;  
 aldehyde 2 is employed in Step A in an amount of from about 1 to about 2 moles  
 15 per mole of piperazine 3; and  
 the  $C_{1-6}$  alkylcarboxylic acid is employed in Step A in an amount of from about 1 to about 2.5 equivalents per equivalent of amino groups present in piperazine 3.

20 16. The process according to claim 15, wherein  
 the tetrahydroborate salt added in Step B is an alkali metal salt or a quaternary ammonium salt of tetrahydroborate;  
 the tetrahydroborate salt is added in Step B in an amount in the range of from about 0.8 to about 4 moles per mole of piperazine 3; and  
 Step B is conducted at a temperature in the range of from about 0 to about 30°C.

25 17. The process according to claim 16, wherein

the catalyst in Step C is employed in an amount in the range of from about 0.01 to about 0.20 moles per mole of piperazine 3 ;

the C<sub>1-6</sub> alkyl alcohol in Step C is employed in an amount of at least about 3 moles per mole of borane complex in the Step B product; and

5 Step C is conducted at a temperature in the range of from about 10 to about 40°C.

18. The process according to claim 14, wherein

by-product water is removed from the reaction mixture of Step A by conducting Step A in the presence of a dehydrating agent comprising molecular sieves;

10 the solvent employed in Step A is an ether;

Step A is conducted at a temperature in the range of from about 10 to about 30°C;

aldehyde 2 is employed in Step A in an amount of from about 1.0 to about 1.5 moles per mole of piperazine 3;

15 the C<sub>1-6</sub> alkylcarboxylic acid is acetic acid employed in Step A in an amount of from about 1.1 to about 2.0 equivalents per equivalent amino groups present in piperazine 3;

the tetrahydroborate salt added in Step B is Na tetrahydroborate added in an amount in the range of from about 0.8 to about 1.3 moles per mole of piperazine 3;

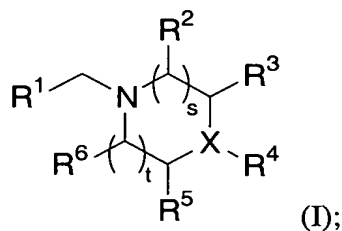
Step B is conducted at a temperature in the range of from about 10 to about 30 °C;

20 the catalyst in Step C is Pt oxide or Pt halide, employed in an amount in the range of from about 0.05 to about 0.15 moles per mole of piperazine 3;

the C<sub>1-6</sub> alkyl alcohol in Step C is methanol or ethanol, employed in an amount in the range of at least about 3 moles per mole of borane complex in the Step B product; and

Step C is conducted at a temperature in the range of from about 15 to about 30°C.

25 19. A process for preparing a compound of Formula (I):

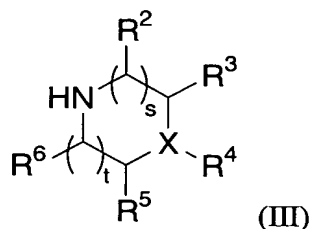


which comprises:

(P) forming a reaction mixture by adding an aldehyde of Formula (II):



a cyclic amine compound of Formula (III):



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claim 1.

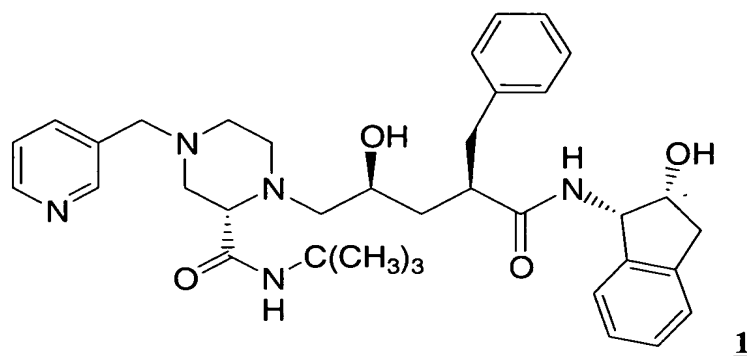
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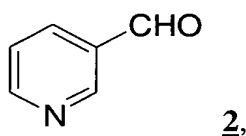
24. The process according to claim 19, wherein the reaction mixture is aged in Step Q at a temperature in the range of from about 5 to about 45°C.

25. A process for preparing Compound 1:

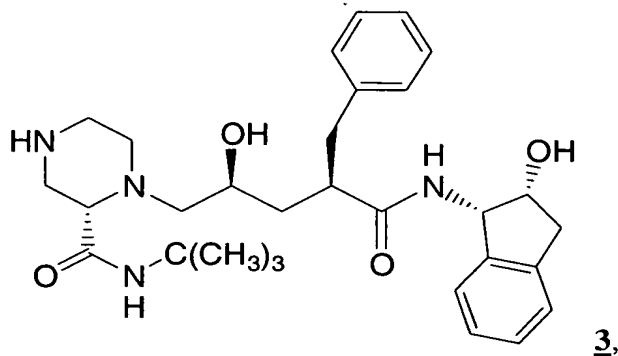


which comprises:

(P) forming a reaction mixture by adding aldehyde 2:



10 piperazine 3:



and optionally a dehydrating agent to a composition comprising an admixture obtained by mixing a tetrahydroborate salt and a C<sub>1-6</sub> alkylcarboxylic acid in an aprotic solvent, wherein the carboxylic acid is employed in the admixture in an amount that is at least sufficient to neutralize

each of the amino groups present in piperazine 3 and to acylate the tetrahydroborate to the extent that free borohydride is substantially absent from the reaction mixture; and

(Q) aging the reaction mixture of Step P to form Compound 1 substantially free of any borane complex thereof.

5

26. The process according to claim 25, wherein:

the tetrahydroborate salt in Step P is Na tetrahydroborate, which is employed in an amount in the range of from about 1 to about 2 moles per mole of piperazine 3;

10 the carboxylic acid in Step P is acetic acid, which is employed in an amount of at least about 1 equivalent per each equivalent of amino groups present in piperazine 3 and in addition at least about 2 equivalents per equivalent of tetrahydroborate;

aldehyde 2 is employed in Step P in an amount of from about 1 to about 2 moles per mole of piperazine 3;

15 a dehydrating agent is present in the reaction mixture of Step P and comprises molecular sieves;

Step P is conducted at a temperature in the range of from about 0 to about 30°C; and

Step Q is conducted at a temperature in the range of from about 5 to about 45°C.